Insulin-Like Growth Factor and Lung Cancer

Vamsidhar Velcheti, MD, and Ramaswamy Govindan, MD*†*

Lung cancer is the leading cause of cancer-related death in the United States. Despite the availability of several cytotoxic and a few molecularly targeted agents, the outlook for patients with advanced non-small cell lung cancer continues to be dismal. Novel approaches are desperately needed. The insulin-like growth factor (IGF) pathway plays an important role in a number of human malignancies contributing to unregulated cell proliferation. The IGF pathway has several targets for therapeutic intervention. Preclinical studies of IGF inhibitors have demonstrated synergism when combined with chemotherapy agents and radiation. Clinical studies are currently ongoing to investigate the safety and efficacy of IGF inhibitors in combination with chemotherapy agents. In this review, we discuss the biology of the IGF pathway and various potential targets for therapy.

Key Words: Insulin-like growth factor, Non-small cell lung cancer.

(*J Thorac Oncol.* 2006;1: 607–610)

Insulin-like growth factor (IGF) is a polypeptide growth factor with functional homology to insulin.[1] IGF has a wide range of metabolic and developmental functions, including embryogenesis and postnatal organogenesis.[2] The IGF signaling pathway plays a critical role in regulating cell proliferation and apoptosis. In this review, we discuss the rationale for targeting the IGF pathway in the treatment of non-small cell lung cancer (NSCLC) (Figure 1).

THE IGF PATHWAY

The IGF system involves complex regulatory network comprising IGF-1 and IGF-2 ligands, six specific high-affinity binding proteins (IGFBP-1 to IGFBP-6) and IGFBP proteases (IGFBP-prs), and IGF-1 and IGF-2 cell surface receptors (IGF-1R and IGF-2R).[3] The half-life and bioavailability of IGF-1 and IGF-2 in circulation varies depending on the affinity and specificity of the IGFBPs in the serum.[4] IGFBP-3, the most critical of the binding protein, binds to 70% to 80% of the IGF-1.[5] Various matrix metalloproteinases (MMPS), often secreted by the tumors, exert proteolytic action on IGFBPs, particularly IGFBP-3, thus increasing the bioavailability of IGFs for receptor-mediated action.[6–9] In addition, IGFBP-3 seems to have a non-IGF mediated antiproliferative and pro-apoptotic action resulting from its association with cell surface proteins or receptors.[10]

Most of the actions of IGF-1 and IGF-2 are mediated by high-affinity ligand binding to IGF-1R, although recent evidence suggests that actions of IGF-2 are also mediated through the high-affinity binding with an insulin receptor (IR) isoform-insulin receptor exon 11 isoform (IR-A).[11] Upon binding of the IGFs to IGF-1R, the receptor's intrinsic tyrosine kinase is activated, resulting in the phosphorylation of the insulin receptor substrates (IRSs).[11–13] The tyrosine-phosphorylated IRS activates phosphatidylinositol-3kinase (PI3K), which catalyzes the conversion of phosphatidylinositol biphosphate (PIP2) to phosphatidylinositol triphosphate (PIP3). V-Akt murine thymoma viral oncogene homolog (Akt) is activated by PIP3. Activated Akt results in a cascade of phosphorylation events in the cytosol, resulting in inactivation of key proteins (Bcl-2 antagonist of cell death, caspase 9, and forkhead transcription factor family) involved in apoptosis.[14] The activation of IGF-1R also modulates the voltage-gated calcium channels, causing transient increase in the intracellular Ca_2^+ level and thereby regulating the nuclear transcription factor, cAMP response element-binding protein (CREB). IGF-2 accentuates the survival and proliferation of lung cancer cells by increasing phosphorylation of CREB via the erk5 pathway.[15,16]

The insulin growth factor-II receptor (IGF2R) lacks signal transduction capability, and its main role is to act as a sink for IGF II and make less IGF II available for binding with IGF-1R.[17]

THE IGF PATHWAY IN LUNG CANCER

Autocrine production of IGF by the tumor cells and high levels of IGF 1 have been reported in the lung tumor tissue.[18,19] Human lung cancer cells also seem to have a higher expression of IGF-2 compared with normal cells and is associated with poor prognosis.[16,20] IGF-2 is overexpressed in both the small cell lung cancer (SCLC) and NSCLC cell lines.[21] Increased expression of IGF-2 in lung cancer results from aberrant regulation of the genomic imprinting mechanism of IGF-2 and mesoderm-specific transcript genes.[22] Genetic aberrations of the M6P/IGF2R locus have been reported in lung cancer cell lines.[23–25] More studies of lung tumor tissue are needed to further elucidate the role of *M6P/IGF2R* gene in the onset and progression of lung cancer.

The IGF-1R seem to be overexpressed in both NSCLC and SCLC.[26–28] Increased metastatic activity was reported in

*Division of Oncology and †Alvin J Siteman Cancer Center, Washington University School of Medicine, St. Louis, Missouri.

Address for correspondence: Ramaswamy Govindan, MD, Division of Medical Oncology, Washington University School of Medicine, 4960 Children's Place, Box 8056, St. Louis, MO 63110. E-mail: rgovinda@im.wustl.edu

ISSN: 1556-0864/06/0107-0607

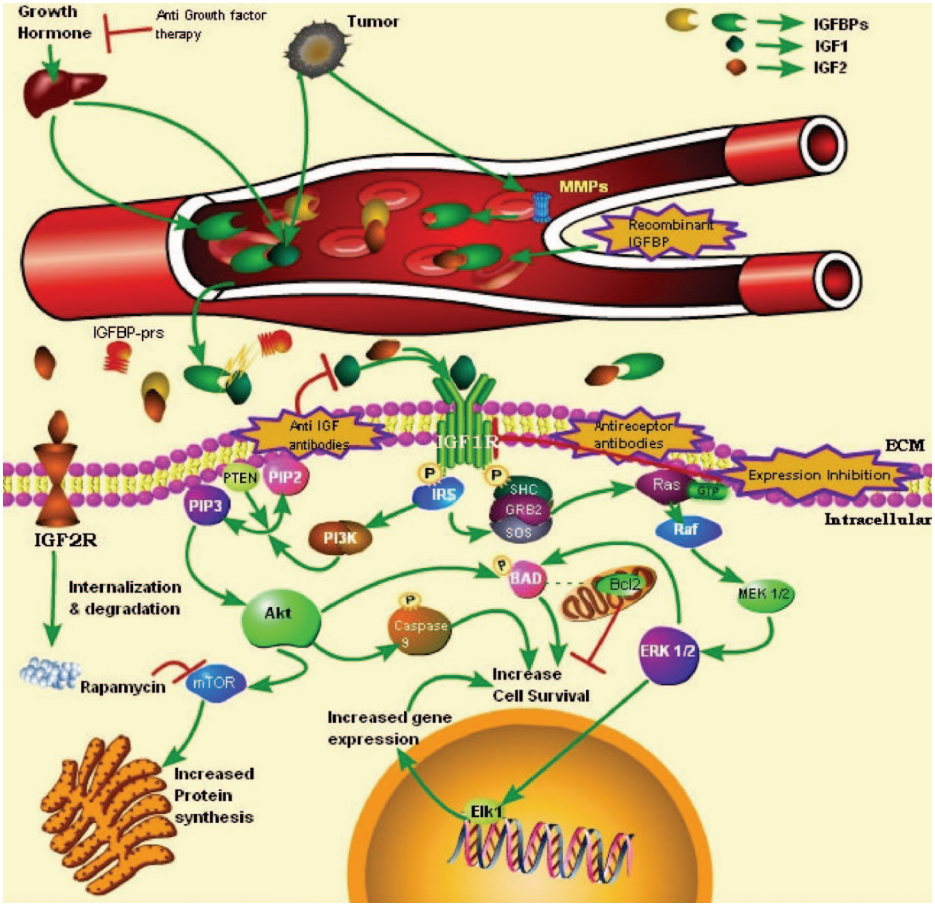

FIGURE 1. *The insulin-like growth factor pathway.*

mice after intrasplenic injection of lung cancer cell lines transfected with IGF-1R receptors.[29]

Decreased expression of IGFBP-3 is also associated with a higher risk of lung cancer indirectly by increasing the bioavailability of IGF ligands.[30–32] IGFBP-3 expression levels are low in one of the four SCLC cell lines and all four of the NSCLC cell lines studied.[33] Hypermethylation of the IGFBP-3 promoter is common (>60%) in NSCLC tissue and is strongly associated with poor prognosis in patients with stage 1 NSCLC (5-year overall survival of patients with IGFBP-3 versus patients without IGFBP-3 hypermethylation is 38.9% versus 64.0%).[30]

A recently published report on a genome wide scan of 1529 patients with lung cancer and 2707 controls in the United Kingdom reported strong evidence that low-penetrance alleles of genes involved in the growth hormone IGF axis are associated with lung cancer susceptibility.[34] In a case control study of 204 consecutive patients with primary lung cancer and 218 age-, sex-, race-, and smoking status-matched control subjects, a higher plasma levels of IGF-1 was associated with an increased risk of lung cancer (OR 2.06; CI 95%).[35] IGF-mediated signaling mechanisms are essential for the proliferation, survival, and metastases of lung cancer cells. Inhibition of IGF activity is associated with decreased tumor growth in vitro.[36–38] There are several ongoing studies exploring the possible therapeutic role of targeting IGF regulation.

THE IGF PATHWAY AS A THERAPEUTIC TARGET

The IGF pathway presents several targets of interest for molecular therapeutics. The possible therapeutic strategies targeting IGF axis-targeted therapies are growth hormone-releasing hormone antagonists, somatostatin analogs, growth hormone (GH) receptor antagonists, IGF-1R antibodies, antibodies directed against IGF ligands, and increasing levels of IGFBP-3.

Clinical trials using somatostatin and other GH receptor antagonists failed to show significant benefit, perhaps because of inadequate reduction in the levels of IGFs. The effect of growth hormone in regulating IGFs of tumor origin is possibly limited; thus, strategies targeting GH may not offer a significant antitumor action.

In vitro studies demonstrated that inhibition of the IGF-1R signaling pathway in human NCLC cells A549 has tumor-inhibiting action and enhances sensitivity to apoptosis-inducing agents.[39,40] Inhibition of IGF-1 signaling using IGF-1R kinase inhibitor NVP-ADW742 has a synergistic increase in the sensitivity of SCLC cell lines to etoposide and

carboplatin.[41] In vitro studies of dual inhibition of IGF-1R (AG 1024) and c-kit activity (AG 1296) produce synergistic activity in SCLC cell lines.[42]

In vitro studies on six NSCLC cell lines' blocking of IGF-1R function with anti-IGF-1R monoclonal antibodies potentiated the cytotoxic effects of radiation in a synergistic fashion in one cell line, in an additive fashion in four cell lines, and in a sub-additive fashion in one cell line.[43] Complete inhibition of tumor growth has been observed when anti-IGF-1R antibody (h7C10) is combined with vinorelbine or an anti-epidermal growth factor receptor antibody in animal models.[40] Clinical trials are currently ongoing to assess the safety and efficacy of human monoclonal antibodies specific for IGF-1R, such as CP-751,871 in advanced NSCLC.

Human monoclonal antibodies specific for IGF-2 have been developed (IgG1 m610), and these antibodies showed good inhibitory activity in in vitro models. IGF-1R is widely expressed, has a broad range of physiological actions, and bears a high homology to the insulin receptor; hence, the use of IGF-1R antibodies could possibly result in more toxicities compared with the use of antibodies directed against IGF ligands.[44]

Transfection of IGFBP-3 into lung cancer cell lines seemed to have profound antitumor effect to the tumor cells in vitro and in vivo.[45,46] Similar results have been found using recombinant human IGFBP-3 in lung carcinoma models using 3LL Lewis lung carcinoma allograft, suggesting a potential therapeutic role of IGFBP-3.[47,48] Thus, IGBP-3 may also represent a potential target.

In summary, the IGF pathway seems to play a critical role in human neoplasia in general and in lung cancer in particular. Clinical trials with IGF inhibitors just begun in NSCLC hopefully will show promising results.

REFERENCES

1. Antoniades HN, Beigelman PM, Pennell RB, Thorn GW, Oncley JL. Insulin-like activity of human plasma constituents. III. Elution of insulin-like activity from cationic exchange resins. *Metabolism* 1958;7:266–268.
2. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev* 1995;16:3–34.
3. Rotwein P. Structure, evolution, expression and regulation of insulin-like growth factors I and II. *Growth Factors* 1991;5:3–18.
4. Clemmons DR. Role of insulin-like growth factor binding proteins in controlling IGF actions. *Mol Cell Endocrinol* 1998;140:19–24.
5. Wolk A. The growth hormone and insulin-like growth factor I axis, and cancer. *Lancet* 2004;363:1336–1337.
6. Fowlkes JL, Serra DM, Bunn RC, Thrailkill KM, Enghild JJ, Nagase H. Regulation of insulin-like growth factor (IGF)-I action by matrix metalloproteinase-3 involves selective disruption of IGF-I/IGF-binding protein-3 complexes. *Endocrinology* 2004;145:620–626.
7. Miyamoto S, Yano K, Sugimoto S, et al. Matrix metalloproteinase-7 facilitates insulin-like growth factor bioavailability through its proteinase activity on insulin-like growth factor binding protein 3. *Cancer Res* 2004;64:665–671.
8. Nakamura M, Miyamoto S, Maeda H, et al. Matrix metalloproteinase-7 degrades all insulin-like growth factor binding proteins and facilitates insulin-like growth factor bioavailability. *Biochem Biophys Res Commun* 2006;333:1011–1016.
9. Mochizuki S, Shimoda M, Shiomi T, Fujii Y, Okada Y. ADAM28 is activated by MMP-7 (matrilysin-1) and cleaves insulin-like growth factor binding protein-3. *Biochem Biophys Res Commun* 2004;315:79–84.
10. Rajah R, Valentinis B, Cohen P. Insulin-like growth factor (IGF)-binding protein-3 induces apoptosis and mediates the effects of transforming growth factor-beta1 on programmed cell death through a p53- and IGF-independent mechanism. *J Biol Chem* 1997;272:12181–12188.
11. Denley A, Cosgrove LJ, Booker GW, Wallace JC, Forbes BE. Molecular interactions of the IGF system. *Cytokine Growth Factor Rev* 2006;16:421–439.
12. Fowden AL. The insulin-like growth factors and feto-placental growth. *Placenta* 2003;24:803–812.
13. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. *Nat Rev Cancer* 2004;4:505–518.
14. Burgering BM, Kops GJ. Cell cycle and death control: long live Forkheads. *Trends Biochem Sci* 2002;27:352–360.
15. Linnerth NM, Baldwin M, Campbell C, Brown M, McGowan H, Moorehead RA. IGF-II induces CREB phosphorylation and cell survival in human lung cancer cells. *Oncogene* 2006;24:7310–7319.
16. Moorehead RA, Sanchez OH, Baldwin RM, Khokha R. Transgenic overexpression of IGF-II induces spontaneous lung tumors: a model for human lung adenocarcinoma. *Oncogene* 2003;22:853–857.
17. Scott CD, Firth SM. The role of the M6P/IGF-II receptor in cancer: tumor suppression or garbage disposal? *Horm Metab Res* 2004;36:261–271.
18. Minuto F, Del Monte P, Barreca A, Alama A, Cariola G, Giordano G. Evidence for autocrine mitogenic stimulation by somatomedin-C/insulin-like growth factor I on an established human lung cancer cell line. *Cancer Res* 1988;48:3716–3719.
19. Minuto F, Del Monte P, Barreca A, et al. Evidence for an increased somatomedin-C/insulin-like growth factor I content in primary human lung tumors. *Cancer Res* 1986;46:985–988.
20. Izycki T, Chyczewska E, Naumnik W, Talalaj J, Panek B, Ossolinska M. Serum levels of IGF-I and IGF-II in patients with lung cancer during chemotherapy. *Exp Oncol* 2004;26:316–319.
21. Reeve JG, Morgan J, Schwander J, Bleehen NM. Role for membrane and secreted insulin-like growth factor-binding protein-2 in the regulation of insulin-like growth factor action in lung tumors. *Cancer Res* 1993;53:4680–4685.
22. Kohda M, Hoshiya H, Katoh M, et al. Frequent loss of imprinting of IGF2 and MEST in lung adenocarcinoma. *Mol Carcinogen* 2001;31:184–191.
23. Kong FM, Anscher MS, Washington MK, Killian JK, Jirtle RL. M6P/IGF2R is mutated in squamous cell carcinoma of the lung. *Oncogene* 2000;19:1572–1578.
24. Tsujiuchi T, Sasaki Y, Tsutsumi M, Konishi Y. Alterations of the M6p/Igf2 receptor gene in lung adenocarcinomas induced by N-nitrosobis(2-hydroxypropyl)amine in rats. *Mol Carcinogen* 2003;36:32–37.
25. Gemma A, Hosoya Y, Uematsu K, et al. Mutation analysis of the gene encoding the human mannose 6-phosphate/insulin-like growth factor 2 receptor (M6P/IGF2R) in human cell lines resistant to growth inhibition by transforming growth factor beta(1) (TGF-beta(1)). *Lung Cancer* 2000;30:91–98.
26. Kaiser U, Schardt C, Brandscheidt D, Wollmer E, Havemann K. Expression of insulin-like growth factor receptors I and II in normal human lung and in lung cancer. *J Cancer Res Clin Oncol* 1993;119:665–668.
27. Rotsch M, Maasberg M, Erbil C, Jaques G, Worsch U, Havemann K. Characterization of insulin-like growth factor I receptors and growth effects in human lung cancer cell lines. *J Cancer Res Clin Oncol* 1992;118:502–508.
28. Schardt C, Rotsch M, Erbil C, Goke R, Richter G, Havemann K. Characterization of insulin-like growth factor II receptors in human small cell lung cancer cell lines. *Exp Cell Res* 1993;204:22–29.
29. Long L, Rubin R, Brodt P. Enhanced invasion and liver colonization by lung carcinoma cells overexpressing the type 1 insulin-like growth factor receptor. *Exp Cell Res* 1998;238:116–121.
30. Chang YS, Kong G, Sun S, et al. Clinical significance of insulin-like growth factor-binding protein-3 expression in stage I non-small cell lung cancer. *Clin Cancer Res* 2002;8:3796–3802.
31. Chang YS, Wang L, Liu D, et al. Correlation between insulin-like growth factor-binding protein-3 promoter methylation and prognosis of patients with stage I non-small cell lung cancer. *Clin Cancer Res* 2002;8:3669–3675.
32. London SJ, Yuan JM, Travlos GS, et al. Insulin-like growth factor I,

IGF-binding protein 3, and lung cancer risk in a prospective study of men in China. *J Natl Cancer Inst* 2002;94:749–754.
33. Reeve JG, Brinkman A, Hughes S, Mitchell J, Schwander J, Bleehen NM. Expression of insulinlike growth factor (IGF) and IGF-binding protein genes in human lung tumor cell lines. *J Natl Cancer Inst* 1992;84:628–634.
34. Rudd MF, Webb EL, Matakidou A, et al. Variants in the GH-IGF axis confer susceptibility to lung cancer. *Genome Res* 2006;16:693–701.
35. Yu H, Spitz MR, Mistry J, Gu J, Hong WK, Wu X. Plasma levels of insulin-like growth factor-I and lung cancer risk: a case-control analysis. *J Natl Cancer Inst* 1999;91:151–156.
36. Taylor JE, Bogden AE, Moreau JP, Coy DH. In vitro and in vivo inhibition of human small cell lung carcinoma (NCI-H69) growth by a somatostatin analogue. *Biochem Biophys Res Commun* 1988;153:81–86.
37. Zia F, Jacobs S, Kull F, Cuttitta F, Mulshine JL, Moody TW. Monoclonal antibody alpha IR-3 inhibits non-small cell lung cancer growth in vitro and in vivo. *J Cell Biochem Suppl* 1996;24:269–275.
38. Lee CT, Wu S, Gabrilovich D, et al. Antitumor effects of an adenovirus expressing antisense insulin-like growth factor I receptor on human lung cancer cell lines. *Cancer Res* 1996;56:3038–3041.
39. Jiang Y, Rom WN, Yie TA, Chi CX, Tchou-Wong KM. Induction of tumor suppression and glandular differentiation of A549 lung carcinoma cells by dominant-negative IGF-I receptor. *Oncogene* 1999;18:6071–6077.
40. Goetsch L, Gonzalez A, Leger O, et al. A recombinant humanized anti-insulin-like growth factor receptor type I antibody (h7C10) enhances the antitumor activity of vinorelbine and anti-epidermal growth factor receptor therapy against human cancer xenografts. *Int J Cancer* 2006;113:316–328.
41. Warshamana-Greene GS, Litz J, Buchdunger E, Garcia-Echeverria C, Hofmann F, Krystal GW. The insulin-like growth factor-I receptor kinase inhibitor, NVP-ADW742, sensitizes small cell lung cancer cell lines to the effects of chemotherapy. *Clin Cancer Res* 2006;11:1563–1571.
42. Camirand A, Pollak M. Co-targeting IGF-1R and c-kit: synergistic inhibition of proliferation and induction of apoptosis in H 209 small cell lung cancer cells. *Br J Cancer* 2004;90:1825–1829.
43. Cosaceanu D, Carapancea M, Castro J, Ekedahl J, Kanter L, Lewensohn R, Dricu A. Modulation of response to radiation of human lung cancer cells following insulin-like growth factor 1 receptor inactivation. *Cancer Lett* 2006;222:173–181.
44. Feng Y, Zhu Z, Xiao X, Choudhry V, Barrett JC, Dimitrov DS. Novel human monoclonal antibodies to insulin-like growth factor (IGF)-II that potently inhibit the IGF receptor type I signal transduction function. *Mol Cancer Ther* 2006;5:114–120.
45. Lee H-Y, Moon H, Chun K-H, et al. Effects of insulin-like growth factor binding protein-3 and farnesyltransferase inhibitor SCH66336 on Akt expression and apoptosis in non-small-cell lung cancer cells. *J Natl Cancer Inst* 2004;96:1536–1548.
46. Hochscheid R, Jaques G, Wegmann B. Transfection of human insulin-like growth factor-binding protein 3 gene inhibits cell growth and tumorigenicity: a cell culture model for lung cancer. *J Endocrinol* 2000;166:553–563.
47. Qingnan Y, Banerjee K, Paterson J, Alami N, Shiry L, Leyland-Jones B. Insulin-like growth factor binding protein-3: single-agent and synergistic effects with chemotherapeutic drugs on solid tumor models [Abstract 1437]. *American Association for Cancer Research*, 2003 July 11–14.
48. Jerome L, Shiry L, Leyland-Jones B. Deregulation of the IGF axis in cancer: epidemiological evidence and potential therapeutic interventions. *Endocr Relat Cancer* 2003;10:561–578.

